Synopsis – Study 14644A

Study Title Interventional, randomised, double-blind, parallel-group, placebo-controlled, active-reference, flexible-dose study of brexpiprazole in patients with acute schizophrenia
Investigators 63 principal investigators at 62 sites in 9 countries *Signatory investigator* – [redacted]
Study Sites 62 sites – 2 in Estonia, 1 in France, 4 in Poland, 10 in Romania, 11 in Russian Federation, 4 in Serbia, 2 in Slovakia, 9 in Ukraine, and 19 in United States
Publications None (as of the date of this report).
Study Period *First patient first visit* – 25 March 2013 (the date when the first *Informed Consent Form* was signed) *Last patient last visit* – 17 December 2014 (the date of the last protocol-specified contact with any patient)
Objectives • *Primary objective*: – to evaluate the efficacy of brexpiprazole (2 to 4 mg/day) *versus* placebo on the treatment of acute schizophrenia • *Secondary objectives*: – to evaluate the efficacy of brexpiprazole (2 to 4 mg/day) *versus* placebo on: • global clinical impression • psychotic symptoms • response rate • personal and social performance • *Exploratory objectives*: – to explore the efficacy of brexpiprazole (2 to 4 mg/day) *versus* placebo on patients' readiness to be discharged – to explore the efficacy of brexpiprazole (2 to 4 mg/day) *versus* placebo on drug attitude – to explore the efficacy of brexpiprazole (2 to 4 mg/day) *versus* placebo on cognition – to explore the efficacy of brexpiprazole (2 to 4 mg/day) *versus* placebo on sleepiness – to explore the efficacy of brexpiprazole (2 to 4 mg/day) *versus* placebo on quality of life • *Pharmacokinetic objective*: – to determine population pharmacokinetic parameters of brexpiprazole (2 to 4 mg/day) and its metabolite, DM-3411 • *Pharmacogenomic objective*: – to evaluate CYP2D6 metabolic profiling • *Safety objectives*: – to evaluate the safety and tolerability of brexpiprazole 2 to 4 mg/day – to explore the effect of brexpiprazole (2 to 4 mg/day) *versus* placebo on suicidality

Study Methodology

- This was an interventional, prospective, multi-national, multi-site, randomised, double-blind, parallel-group, placebo-controlled, active-reference, flexible-dose study.
- The study consisted of:
  - Screening Period – 1 to 14-day period from screening to randomisation. Hospitalisation began after signing of the *Informed Consent Form* unless the patient was already hospitalised.
  - Treatment Period – 6-week double-blind treatment period with placebo, brexpiprazole (2 to 4 mg/day), or quetiapine extended release (quetiapine XR; hereafter referred to as quetiapine; 400 to 800 mg/day). Patients randomised to brexpiprazole received 1 mg/day on Day 1, 2 mg/day on Day 2, 3 mg/day on Day 3 (uptitration); the dose could be adjusted from Day 4 onwards to 2, 3, or 4 mg/day to optimise the clinical effect and tolerability. Patients randomised to quetiapine received 300 mg/day on Day 1, 600 mg/day on Days 2 and 3 (uptitration); the dose could be adjusted from Day 4 onwards to 400, 600, or 800 mg/day to optimise the clinical effect and tolerability.
  - Safety Follow-up Period – 30-day period after completion of the study or after withdrawal from the study for patients not continuing in the open-label extension study (Study 14644B)

Number of Patients Planned

465 patients were planned for randomisation: 155 in each treatment group.

Diagnosis and Main Selection Criterion

Inpatients with a primary diagnosis of schizophrenia according to DSM-IV-TR™ criteria, who:

- had an acute exacerbation psychotic symptoms evidenced by a Positive and Negative Syndrome Scale (PANSS) total score ≥80, PANSS single item score ≥4 for at least two of the following items: hallucinatory behaviour, unusual thought content, conceptual disorganisation, or suspiciousness/persecution, and a Clinical Global Impression – Severity of Illness (CGI-S) score ≥4 at the Screening Visit and at the Baseline Visit
- were willing to be hospitalised from the Screening Visit until the Completion/Withdrawal Visit
- were ≥18 and ≤65 years of age

Investigational Medicinal Product, Dose and Mode of Administration, Batch Numbers

Brexpiprazole – 1, 2, 3, or 4 mg; tablets, orally

- *Brexpiprazole 1 mg* – batch No. 11L88A001, 13A97A001
- *Brexpiprazole 2 mg* – batch No. 12A73A002, 13A98A002
- *Brexpiprazole 3 mg* – batch No. 12A74A003, 13A99A003
- *Brexpiprazole 4 mg* – batch No. 12A75A004, 13A00A004

Reference Therapies, Doses and Modes of Administration, Batch Numbers

Placebo – tablets, orally; batch No. 11L78P005, 13A92P005A

Placebo – capsules, orally; batch No. E08765-001E

Quetiapine (Seroquel XL®/XR®) – 300 or 400 mg encapsulated tablets, orally

- *Encapsulated quetiapine 300 mg tablets* – batch No. E009717-0001E, E009717-0042E, P009717-0027E
- *Encapsulated quetiapine 400 mg tablets* – batch No. E009717-0002E, E009717-0043E, E009717-0044E, P009717-0028E

Duration of Treatment

6 weeks

Efficacy Assessments • PANSS • CGI-S • Clinical Global Impression – Global Improvement (CGI-I) • Personal and Social Performance Scale (PSP) • Readiness to Discharge Questionnaire (RDQ) • Drug Attitude Inventory - 10 Item (DAI-10) • CogState Cognitive Test Battery • Schizophrenia Quality of Life Scale (S-QoL) • Karolinska Sleepiness Scale (KSS)
Pharmacokinetic Assessments • blood sampling for plasma quantification of brexpiprazole and its metabolite DM-3411 • blood sampling for CYP2D6 assessment
Safety Assessments • Adverse events (AEs), clinical safety laboratory tests, vital signs, weight/body mass index (BMI), waist circumference, electrocardiograms (ECGs), and physical examinations • Columbia Suicide Severity Rating Scale (C-SSRS) • Simpson Angus Scale (SAS) • Barnes Akathisia Scale (BARS) • Abnormal Involuntary Movement Scale (AIMS)

Endpoints

- *Primary endpoint*:
  - psychotic symptoms:
    - change from baseline to Week 6 in PANSS total score
- *Key secondary endpoint*:
  - global clinical impression:
    - change from baseline to Week 6 in CGI-S score
- *Secondary endpoints*:
  - global clinical impression:
    - CGI-I score at Week 6
  - psychotic symptoms:
    - change from baseline to Week 6 in PANSS positive subscale score
    - change from baseline to Week 6 in PANSS negative subscale score
    - change from baseline to Week 6 in PANSS general psychopathology subscale score
    - change from baseline to Week 6 in PANSS excited component score
    - change from baseline to Week 6 in PANSS marder factor scores: negative symptoms
    - change from baseline to Week 6 in PANSS marder factor scores: positive symptoms
    - change from baseline to Week 6 in PANSS marder factor scores: disorganized thought
    - change from baseline to Week 6 in PANSS marder factor scores: uncontrolled hostility/excitement
    - change from baseline to Week 6 in PANSS marder factor scores: anxiety/depression
    - discontinuation for lack of efficacy during the study
  - response at Week 6, defined as a reduction of ≥30% from baseline in PANSS total score OR a CGI-I score of 1 or 2
  - personal and social performance
    - change from baseline to Week 6 in PSP total score
    - PSP functional remission at Week 6, defined as a PSP total score ≥71
    - PSP functional response at Week 6, defined ≥10 point improvement from Baseline on the PSP total score
    - PSP Domain D: disturbing and aggressive behaviours at Week 6, categorised as "*aggressive*" (corresponding to *mild*, *manifest*, *marked*, *severe*, or *very severe*) or "*non-aggressive*" (corresponding to *absent*)
- *Exploratory endpoints*:
  - readiness to discharge:
    - time to discharge readiness in RDQ
  - drug attitude inventory:
    - change from baseline to Week 6 in DAI-10 total score
    - DAI-10 response, defined as a DAI-10 total score ≥0
  - cognition:
    - change from baseline to Week 6 in the composite Z-score
    - change from baseline to Week 6 in Groton Maze Learning Task
    - change from baseline to Week 6 in Detection Task
    - change from baseline to Week 6 in Identification Task
    - change from baseline to Week 6 in One Card Learning Task

Endpoints (continued)

- quality of life:
  - change from baseline to Week 6 in S-QoL total score
  - change from baseline to Week 6 in S-QoL Psychological Well-Being
  - change from baseline to Week 6 in S-QoL Self-esteem
  - change from baseline to Week 6 in S-QoL Family Relationships
  - change from baseline to Week 6 in S-QoL Relationships with Friends
  - change from baseline to Week 6 in S-QoL Resilience
  - change from baseline to Week 6 in S-QoL Physical Well-being
  - change from baseline to Week 6 in S-QoL Autonomy
  - change from baseline to Week 6 in S-QoL Sentimental Life
- sleepiness
  - change from baseline to Week 6 in KSS total score

- *Safety endpoints*:
  - adverse events
  - absolute values and changes from baseline in clinical safety laboratory tests, vital signs, weight, BMI, waist circumference, and ECG parameters
  - potentially clinically significant (PCS) clinical safety laboratory test values, vital signs, weight changes, and ECG parameter values
  - C-SSRS categorisation based on Columbia Classification Algorithm for Suicide Assessment (C-CASA) definitions
  - SAS, BARS, and AIMS scores

Statistical Methodology

- The following analysis sets were used:
  - *all-patients-randomised set* (APRS) – all randomised patients
  - *all-patients-treated set* (APTS) – all patients in the APRS who took at least one dose of double-blind IMP
  - *full-analysis set* (FAS) – all patients in the APTS who had a baseline assessment and at least one post-baseline assessment of the PANSS total score; covering the period until withdrawal/completion
- Unless otherwise indicated, the efficacy analyses were based on the FAS and the safety analyses were based on the APTS.
- For all efficacy analyses the primary comparison is the difference between brexpiprazole 2 to 4 mg/day and placebo at Week 6. All efficacy analyses are also presented for quetiapine compared with placebo.
- *Primary efficacy analysis:*
  - The change from baseline in the PANSS total score was analysed using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) approach. The model included pooled site, visit, and treatment as fixed effects, baseline score as a continuous covariate, treatment-by-visit interaction, and baseline score-by-visit interaction.
  - Subgroup analyses of the primary analysis were conducted for the following subgroups:
    - age (<55, ≥55)
    - sex (men, women)
    - race (White, all other races than White)
    - region (US, Europe)
    - time since first diagnosis (<5 years, 5 to <10 years, ≥10 years)
  - Sensitivity analyses were performed using:
    - a delta method assuming that patients withdrawing due to adverse events, due to lack of efficacy, OR due to adverse events or lack of efficacy would have a loss of effect of delta
    - placebo-based multiple imputation (PMI) assuming that patients withdrawing due to adverse events, due to lack of efficacy, OR due to adverse events or lack of efficacy would continue with a trajectory similar to patients receiving placebo
    - an MMRM approach similar to the primary analysis, including the follow-up efficacy data for patients withdrawn from treatment
    - an analysis of covariance (ANCOVA) model estimating the effect at Week 6, using both observed cases (OC) and last observation carried forward (LOCF), including pooled site and treatment as fixed effects and baseline score as covariate
- *Key secondary efficacy analysis*
  - The change from baseline in CGI-S score was analysed using an MMRM approach similar to the primary analysis. The baseline CGI-S was used as the baseline score covariate.
  - A sensitivity analysis for the key secondary analysis was performed including the follow-up CGI-S data for patients withdrawn from treatment, using an MMRM approach similar to the primary analysis.
- *Testing strategy:*
  - The overall significance level was 0.05. The primary and the key secondary endpoints were tested hierarchically. Only if the primary endpoint was statistically significant would confirmatory testing continue with the key secondary endpoint.

Statistical Methodology (continued)

- *Secondary efficacy analyses:*
  - The continuous secondary endpoints (PANSS subscale score, PANSS excited component score, PANSS marder factor scores, and PSP total score) were analysed using an MMRM approach similar to the primary analysis with the relevant baseline score as a covariate. CGI-I was analysed using a similar model with the CGI-S baseline score as a covariate.
  - The time to discontinuation for lack of efficacy based on the primary reason for withdrawal was presented using a Nelson Aalen curve. The time to discontinuation for lack of efficacy was analysed using Cox's proportional hazards model including the baseline PANSS total score as a covariate and treatment as a factor. The hazard ratio for brexpiprazole *versus* placebo was estimated from the model.
  - The binary variables (response, PSP functional response, and PSP functional remission) were analysed using logistic regression, including the baseline PANSS total score as a covariate and treatment as a factor. The odds ratios for brexpiprazole *versus* placebo were estimated from the model. The model was applied to patients with Week 6 assessments, to all patients using last assessment, and to all patients using non-response imputation.
  - Descriptive statistics are presented by visit for the categorical variable PSP domain D. A shift table displaying shifts in aggression status from baseline to the Week 6 Visit is provided by treatment including the numbers and percentages of patients.
- *Exploratory efficacy analyses:*
  - The change from baseline in the DAI-10 score and KSS total score were analysed using an MMRM approach similar to the primary analysis with the relevant baseline score as covariate.
  - Furthermore the DAI-10 response was analysed using a logistic regression model, including the DAI-10 baseline score as a covariate and treatment as a factor. The logistic regression model was performed for patients with Week 6 assessments, for all patients using last assessment, and for all patients using non-response imputation. The odds ratios for brexpiprazole *versus* placebo was estimated from the model.
  - The change from baseline to Week 6 in the CogState cognitive test battery and the S-QoL total score was analysed using an ANCOVA model, including site and treatment as fixed effects, and the relevant baseline score as a continuous covariate. The mean difference between brexpiprazole and placebo was estimated from the model based on the least squares means. The ANCOVA model was applied to patients with Week 6 assessments and to all patients using last assessment.
  - The time to readiness to discharge was presented using a Nelson Aalen curve. Time to readiness for discharge in the RDQ was analysed using a Cox proportional hazard model including the baseline PANSS total score as a covariate and treatment as a factor. The hazard ratio for brexpiprazole *versus* placebo was estimated from the model.
- *Safety analyses:*
  - The overall incidences of adverse events, serious adverse events (SAEs) and adverse events leading to withdrawal were summarised by primary system organ class (SOC) and preferred term for each treatment group.
  - Absolute values and changes from baseline were summarised by visit and last assessment for clinical safety laboratory tests, vital signs, weight (BMI), waist circumference, and ECGs using descriptive statistics. Values outside the reference ranges, as well as PCS values, were flagged and summarised.
  - The C-SSRS data were summarised by treatment and time period both for the raw data and by the C-CASA categories.
  - Descriptive statistics of absolute values and changes from baseline for the SAS total score, BARS item 4 (Global Clinical Assessment of Akathisia) score, and AIMS total score were summarised by visit and treatment group. The change from baseline in SAS total score, BARS item 4 score, and AIMS total score were analysed using an MMRM approach similar to that described for the primary analysis with the relevant baseline score as covariate. The single-item scores for BARS items 1, 2, and 3 and AIMS items 8 to 12 were summarised by visit and treatment group.

Patient Disposition and Analysis Sets

- Patient disposition is summarised below:

	Placebo		Brexpiprazole		Quetiapine		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients randomised	163		151		154		468	
Patients treated (all-patients-treated set [APTS])	161		150		153		464	
Patients completed	108	(67.1)	113	(75.3)	122	(79.7)	343	(73.9)
Patients withdrawn	53	(32.9)	37	(24.7)	31	(20.3)	121	(26.1)
Primary reason for withdrawal:								
Adverse event(s)	11	(6.8)	14	(9.3)	4	(2.6)	29	(6.3)
Lack of efficacy	24	(14.9)	19	(6.7)	11	(7.2)	45	(9.7)
Other	18	(11.2)	13	(8.7)	16	(10.5)	47	(10.1)
Analysis sets:								
APTS	161		150		153		464	
Full-analysis set (FAS)	159		150		150		459	

Demography and Baseline Characteristics of the Study Population

- The treatment groups were similar with respect to age, sex, and race distribution: the mean age of the patients was 41 years, there were slightly more men than women (overall 57% versus 43%), and approximately three-quarters of the patients in each treatment group were White.
- The mean height, weight, BMI, and waist circumferences were approximately 171cm, 79kg, 27kg/m^2, and 92cm, respectively, with no clinically relevant differences between the treatment groups.
- Schizophrenia history at baseline was similar across the treatment groups. Overall, the mean time (years) since the first diagnosis for schizophrenia was 13.6 years and the mean time (years) since the first antipsychotic treatment was 14.1 years. The majority (>77%) had had the schizophrenia diagnosis for at least 5 years.
- There were no clinically relevant differences in mean baseline efficacy scores between the treatment groups. The patients were *markedly ill* at study entry, with a mean overall PANSS total score of 98 and a mean overall CGI-S score of 4.96. The PSP total score was approximately 43, indicating that the patients had *marked* or *severe* difficulties in several areas of functioning, and the S-QoL total score was approximately 43, indicating that the patients had *markedly* impaired health-related quality of life.

Efficacy Results

- Change from baseline in PANSS total score at Week 6 did not show statistical significance when comparing brexpiprazole to placebo (p=0.056). The change from baseline in PANSS total score favoured brexpiprazole compared to placebo (p<0.05) at Weeks 2, 3, and 4.
- The active reference for the study, quetiapine, separated from placebo on the primary efficacy analysis thus validating the study methodology and patient population.
- The efficacy results of the primary (PANSS total score), key secondary (CGI-S score), PSP, CGI-I, and responder analyses at Week 6 are summarised below:

Efficacy Variable	n	Placebo	n	Brexpiprazole	n	Quetiapine
Δ PANSS total score	111	-15.9	114	-20.0 (p=0.056)	123	-24.0 (p<0.001)
Δ CGI-S score	111	-0.9	114	-1.2 (p<0.05)	123	-1.4 (p<0.001)
Δ PSP total score	112	9.4	114	13.0 (p<0.05)	126	15.3 (p<0.001)
CGI-I score	111	3.0	114	2.7 (p<0.05)	123	2.5 (p<0.001)
Responders[a]	51	32.1%	73	48.7% (p<0.01)	94	62.7% (p<0.001)

Δ = change from baseline (MMRM)
mean values and p-values *versus* placebo are presented
[a]Defined as a reduction of ≥30% from baseline in PANSS total score at Week 6 or a CGI-I score of 1 or 2 at Week 6 (last assessment, LREG)

Efficacy Results (continued)

- In the sensitivity analyses of the primary efficacy variable, brexpiprazole separated from placebo ($p<0.05$) in the ANCOVA, LOCF ($p=0.025$), ANCOVA, OC ($p=0.026$), and multiple imputation assuming missing at random (MAR) (delta=0) when pooled site was used as a factor in the analysis *(post-hoc*, $p=0.0496$). For all other sensitivity analyses, $p>0.05$.
- For the key secondary efficacy endpoint (change from baseline in CGI-S score), the patients in the brexpiprazole group separated from the placebo group at Week 6 ($p=0.014$).
- Brexpiprazole separated from placebo on the PANSS positive symptoms subscale and the Marder Factor score for positive symptoms (both $p<0.05$), however, for the other PANSS subscale scores, $p>0.05$.
- The patients in the brexpiprazole group had numerically lower scores on the CGI-I scale than patients in the placebo group indicating greater improvement throughout the Treatment Period. The difference in the brexpiprazole and placebo groups in CGI-I score at Week 6 was -0.3 ($p=0.029$) with separation from placebo in favour of brexpiprazole at Weeks 1 through 4 and at Week 6 ($p<0.05$; MMRM).
- Regarding treatment response at Week 6, a higher proportion of patients in the brexpiprazole group were responders compared with the placebo group when missing response was imputed using for last assessment (48.7% *versus* 32.1%; $p=0.003$).
- In exploratory analysis, a numerical advantage was found for patients in the brexpiprazole group compared to the placebo group in the RDQ, DAI-10, CogState, and KSS measures, however, $p>0.05$.
- Health-related quality of life measured by the S-QoL improved substantially from baseline to Week 6 in the brexpiprazole group compared to the placebo group. In the last assessment, ANCOVA, a separation from placebo ($p<0.05$) in favour of brexpiprazole was seen for S-QoL total score and for all subscale scores with the exception of the *resilience* subscale.

Safety Results

- The adverse event incidence is summarised below:

	Placebo		Brexpiprazole		Quetiapine	
	n	(%)	n	(%)	n	(%)
Patients treated	161		150		153	
Patients who died	0		0		0	
Patients with serious adverse events (SAEs)	6	(3.7)	8	(5.3)	2	(1.3)
Patients with treatment-emergent adverse events (TEAEs)	88	(54.7)	81	(54.0)	101	(66.0)
Patients with TEAEs leading to withdrawal	17	(10.6)	15	(10.0)	4	(2.6)
Total number of SAEs	7		8		2	
Total number of TEAEs	178		202		295	

- No deaths occurred and the number of patients with one or more SAEs was low: 6 patients (3.7%) in the placebo group, 8 patients (5.3%) in the brexpiprazole group, and 2 patients (1.3%) in the quetiapine group. Four SAEs (angiodema, type II diabetes mellitus, suicide attempt, and grand mal convulsion) in 4 patients (all in the brexpiprazole group) were considered *possibly* or *probably related* to IMP .
- A little more than half of the patients in the placebo and brexpiprazole groups and approximately two-thirds of the patients in the quetiapine group had one or more TEAEs. The incidence of TEAEs leading to withdrawal was similar in the placebo and brexpiprazole groups (11% and 10%, respectively) and lower in the quetiapine group (3%). The TEAEs leading to withdrawal in ≥2 patients in any treatment group were schizophrenia (10 patients) and psychotic disorder (3 patients) in the placebo group and schizophrenia in the brexpiprazole (7 patients) and quetiapine (3 patients) groups.
- During the Treatment Period, the TEAEs with an incidence ≥5% in the brexpiprazole group and for which the incidence was numerically higher than that in the placebo group, comprised insomnia (8.7% *versus* 6.2%), akathisia (6.0% *versus* 2.5%), and weight increased (5.3% *versus* 3.7%). The TEAEs with an incidence ≥5% in the quetiapine group and for which the incidence was numerically higher than that in the placebo group, comprised somnolence (22.2% *versus* 5.0%), weight increased (13.1% *versus* 3.7%), dizziness (11.8% *versus* 0.6%), dry mouth (8.5% *versus* 1.2%), and sedation (5.2% *versus* 3.1%).
- TEAEs with an incidence ≥5% in either treatment group in the Treatment Period are summarised below:

Preferred Term	Placebo		Brexpiprazole		Quetiapine	
(MedDRA Version 16.1)	n	(%)	n	(%)	n	(%)
Patients treated	161		150		153	
Insomnia	10	(6.2)	13	(8.7)	4	(2.6)
Akathisia	4	(2.5)	9	(6.0)	6	(3.9)
Schizophrenia	15	(9.3)	9	(6.0)	5	(3.3)
Headache	11	(6.8)	8	(5.3)	9	(5.9)
Weight increased	6	(3.7)	8	(5.3)	20	(13.1)
Somnolence	8	(5.0)	7	(4.7)	34	(22.2)
Dizziness	1	(0.6)	4	(2.7)	18	(11.8)
Sedation	5	(3.1)	4	(2.7)	8	(5.2)
Dry mouth	2	(1.2)	2	(1.3)	13	(8.5)

- The majority of the patients with TEAEs had TEAEs that were either *mild* or *moderate*. The overall incidence of *severe* TEAEs was 6% in the placebo group, 9% in the brexpiprazole group, and 4% in the quetiapine group.
- One patient in the brexpiprazole group had a non-fatal *suicide attempt* reported as an SAE. Otherwise, based on the C-SSRS data, no patient had suicidal ideation with an intent or plan, nor had any patient suicidal behaviour involving either a preparatory act, or an aborted or actual attempt.

Safety Results (continued)

- The proportion of patients with extrapyramidal symptoms (EPS)-related TEAEs was 6% in the placebo group, 11% in the brexpiprazole group, and 9% in the quetiapine group. In each treatment group, the EPS-related TEAEs with an incidence ≥2% were akathisia (4 patients) in the placebo group, akathisia (9 patients) and tremor (5 patients) in the brexpiprazole group, and tremor (7 patients) and akathisia (6 patients) in the quetiapine group. Four patients had EPS-related adverse events that led to withdrawal: 1 in the placebo group (psychomotor hyperactivity) and 3 in the brexpiprazole group (psychomotor hyperactivity; musculoskeletal stiffness, and tremor).
- The incidence of somnolence-related TEAEs was similar in the brexpiprazole (7%) and placebo groups (7%) and higher in the quetiapine group (26%). None of the patients withdrew due to somnolence-related TEAEs.
- In general, the scores on the SAS, BARS, and AIMS safety rating scales were low with minor fluctuations over time. There were no deterioration of the EPS-related symptoms and no clinically relevant differences between any of the treatment groups.
- The mean change from baseline to Week 6 in prolactin decreased in the placebo and quetiapine groups (by 44.68 mIU/L and 128.21 mIU/L, respectively); in the brexpiprazole group it increased by 13.77 mIU/L. No clinically relevant patterns were seen with respect to the mean changes in clinical safety laboratory test values (including fasting glucose and lipid values), vital signs, weight, or ECG parameter values, and the incidences of PCS values were comparable between the placebo and brexpiprazole groups. Weight gain was more prominent in the quetiapine group (2.5kg) than in the placebo (0.5kg) or brexpiprazole groups (1.6kg) at Week 6. Furthermore, quetiapine induced a slight elevation in the heart rate (which was reflected in some of the ECG parameters) and a slight elevation in lipid values (cholesterol, low density lipoprotein (LDL), cholesterol, and triglycerides).
- Overall, brexpiprazole was safe and well tolerated.

Conclusions

- Based on the pre-specified testing strategy in this study, treatment with brexpiprazole did not reach statistical significance in the primary efficacy variable, the change from baseline in PANSS total score at Week 6, compared to placebo. There was evidence of treatment effects in a number of sensitivity analyses of the primary efficacy variable.
- The study methodology and patient population were validated based on the separation from placebo in PANSS total score seen with quetiapine, the active reference for this study.
- Patients in the brexpiprazole group separated from placebo on the PANSS positive symptom subscale, Marder Factor positive symptom subscale, CGI-S score, CGI-I score, the percentage of responders, PSP total score, and on several dimensions of the S-QoL at Week 6, supporting the treatment effect of brexpiprazole.
- Based on the totality of the data in this study, the results suggest a treatment effect of brexpiprazole compared to placebo where patients experienced benefits in several facets of schizophrenic symptom reduction as well as improved psychosocial functioning and health-related quality of life.
- No risk of suicidality was observed in the brexpiprazole group compared to the placebo group based on the C-SSRS and adverse event profile.
- Overall, brexpiprazole was safe and well tolerated in patients with schizophrenia.

Report Date
15June2015

This study was conducted in compliance with the principles of *Good Clinical Practice*.